

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>X16080</b>	<b>FOR FURTHER ACTION</b> <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/US2005/007052</b>	International filing date (day/month/year) <b>08/03/2005</b>	(Earliest) Priority Date (day/month/year) <b>12/03/2004</b>
Applicant  <b>ELI LILLY AND COMPANY</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/007052

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 C07D405/12 C07D307/91 C07D491/04 A61K31/335  
A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	✓ EP 0 569 802 A (MERCK PATENT GMBH) 18 November 1993 (1993-11-18) the whole document	1-21
A	✓ US 4 678 779 A (MEYERS ET AL) 7 July 1987 (1987-07-07) the whole document	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## ° Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

11 August 2005

Date of mailing of the international search report

22/08/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Grassi, D

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/007052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0569802	A	18-11-1993	DE 4215213 A1 11-11-1993
			AT 168368 T 15-08-1998
			AU 3834193 A 11-11-1993
			BR 1100581 A3 01-08-2000
			CA 2095797 A1 10-11-1993
			CN 1079219 A ,C 08-12-1993
			CZ 9300823 A3 16-02-1994
			DE 59308763 D1 20-08-1998
			DK 569802 T3 19-04-1999
			EP 0569802 A1 18-11-1993
			ES 2121030 T3 16-11-1998
			HK 1011990 A1 24-03-2000
			HU 70172 A2 28-09-1995
			JP 3210771 B2 17-09-2001
			JP 6049022 A 22-02-1994
			NO 931681 A ,B, 10-11-1993
			PL 298845 A1 10-01-1994
			RU 2125041 C1 20-01-1999
			SK 46893 A3 06-04-1994
			US 5532266 A 02-07-1996
			ZA 9303222 A 08-12-1993
US 4678779	A	07-07-1987	US 4910152 A 20-03-1990

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

12 DEC 2005 / 12 JAN 2006

X16080

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**

See paragraph 2 below

International application No.  
PCT/US2005/007052

International filing date (day/month/year)  
08.03.2005

Priority date (day/month/year)  
12.03.2004

International Patent Classification (IPC) or both national classification and IPC  
C07D409/12, C07D405/12, C07D307/91, C07D491/04, A61K31/335, A61P3/04

Applicant  
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1 (a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized Officer

Grassi, D

Telephone No. +49 89 2399-8499



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/007052

---

**Box No. I Basis of the opinion**

---

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/007052

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 16-20

because:

- ☒ the said international application, or the said claims Nos. (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/007052

---

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

---

**1. Statement**

Novelty (N)	Yes: Claims	1-21
	No: Claims	
Inventive step (IS)	Yes: Claims	1-21
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-15,21
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

Reference is made to the following documents:

D1: EP-A-0 569 802

**Re Item III**

Claims 15-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

- 1) The subject-matter of present claims 1-21 is new (Article 33(2) PCT).
- 2) The subject-matter of claims 1-21 involves an inventive step (Article 33(3) PCT).

The closest prior art is represented by D1 relating to compounds with affinity to the kappa receptor. The most relevant compounds of D1 are the xanthene derivatives disclosed in example 5.

The present compounds differ from the compounds of D1 in the two mandatory substituents on the tricyclic ring system.

The technical problem underlying the present application is seen in the provision of alternative agents having affinity to opioid receptors.

In view of the test results disclosed on the pages 22/23, the problem appears to be solved.

The prior art does not appear to prompt the skilled person to the presently claimed compounds. Consequently, inventive activity appears to be involved.

Therefore, the subject-matter of the claims relating to a pharmaceutical composition or to the use of the compounds also fulfill this requirement.



**REMARK**

- 1) Several examples (e.g. examples 8-12 or 15-19) appear not to fall within the generic definition of claim 1 (with respect to residues R1/R2).
  - 1.1) The same applies to several residues mentioned in dependent claim 11.
- 2) The term prodrug does not satisfy the requirements of Article 6 PCT.  
The term is to be seen as a functional feature. Functional features are, however, allowable only if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to a person skilled in the art and which do not require undue experimentation (cf. Guidelines, II, 5.35).